Bacteriophages as therapeutic tools

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Introduction and Objectives

Increasing antibiotic resistances among bacteria has exposed the urge to find alternatives like the use of bacteriophages. To speculate about the future implementation of phages as therapeutic tools this work's objectives are:

- Explain bacteriophages characteristics, positive and negative aspects.
- last studies on the subject and other potential uses.
- Review the current regulation.

Figure 1. Micrograph of multiple bacteriophages attached to a bacterial cell wall by Dr Graham Beards.

Bacteriophages

Bacteriophages are **viruses that infect bacteria** and they were discovered a century ago.

Phages are the most common entities in nature.

Most identified phages pertain to the ***Caudovirales*** order (dsDNA genome with a tailed morphology).

Bacteriophages have two kinds of cycle:

- Lytic cycle is associated with virulent phages. Usually, it ends with the bacterium lysis and release of the new phages.
- Lysogenic cycle is more frequent in tempered phages and it doesn't imply lysis.

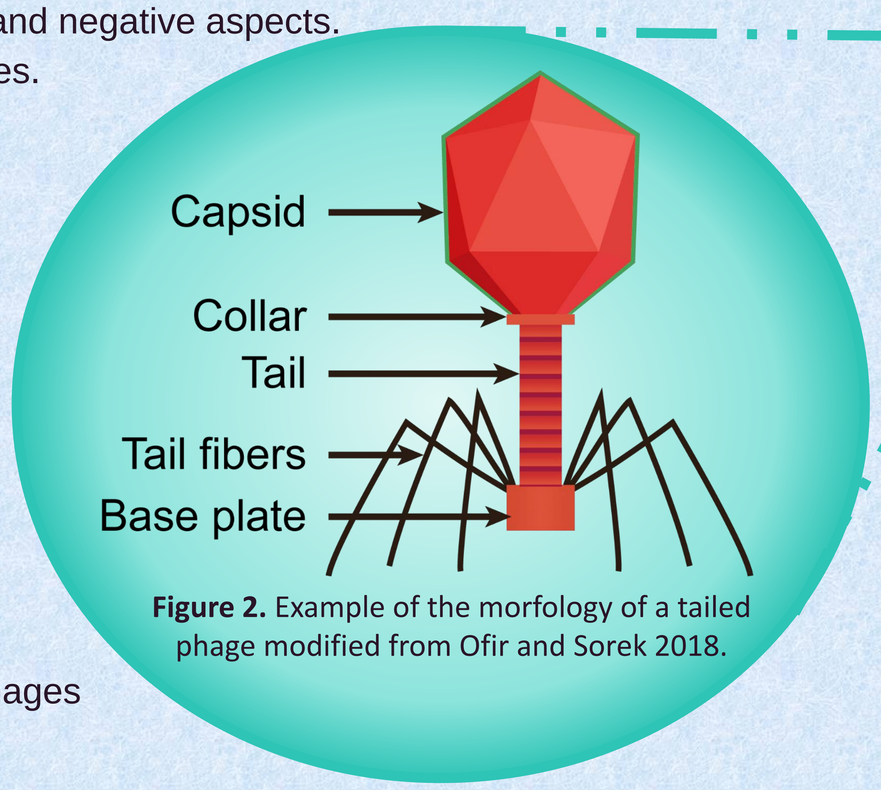

Figure 2. Example of the morfology of a tailed phage modified from Ofir and Sorek 2018.

Another approach are **phage derived proteins**: Endolysins, depolymerase, endolysins, holins, receptor-binding proteins, murein hydrolases, anti-CRISPR proteins...

They can be combined quite successfully with antibiotics (**Table 1**).

Table 1. Possible effects of combining antibiotics and bacteriophages (Torres-Barceló and Hochberg 2016)	
Simultaneous administration	Bacteria are successfully eliminated.
	Resistant bacteria to both treatments emerge but with slow growth and loss of pathogeny.
Sequential administration	Bacteria resistant to both would be double mutant which is notably rare, and growth would be reduced.

Uses in the agro-food context

The use of phages and their derived proteins is very promising in the agro-food context:

- **Against bacterial crop diseases**
- In livestock farming and aquaculture **reducing zoonotic bacteria in animals** including as **prophylactics**.
- **Disinfectants of equipment, contact surfaces and even in raw products** against *Listeria monocytogenes*, *Salmonella enterica* and *Escherichia coli*.
- **Biopreservation** to extend the shelf life of manufactured foods.

Advantages

- ✓Effectivity against gram positive as well as gram negative.
- ✓Activity against multidrug resistant bacteria.
- ✓Specificity.
- ✓Few side effects have been reported till now.
- ✓Wide distribution.
- ✓Some phages can disrupt bacterial biofilms.
- ✓Immunomodulatory effects without causing immune deficits.
- ✓Relative low development costs.

Disadvantages

- X Need to define optimal dose, route of administration, frequency, and duration of treatment.
- X Possible inactivation by immune system.
- X Need to determine accurately the etiology of the pathogen bacteria.
- X DNA transference can lead to more virulent or more resistant bacteria.
- X Release of harmful bacterial substances due to the bacterial lysis like endotoxins from gram-negative bacteria.
- X Emergence of bacterial resistance against phages.

Regulation

Some phage preparations have already been approved for the EFSA and FDA in the food processing industry.

In the EU and in the US the therapeutic use of phages fall under unauthorized medicinal products restricting it to unique situations.

Because of their nature it is hard to make them fit under the same regulations than conventional drugs.

The implementation of new regulations in the EU is required.

References:

Ofir G, Sorek R. 2018. Contemporary Phage Biology: From Classic Models to New Insights. Cell. 172(6):1260–1270. doi:10.1016/j.cell.2017.10.045.

Torres-Barceló C, Hochberg ME. 2016. Evolutionary Rationale for Phages as Complements of Antibiotics. Trends Microbiol. 24(4):249–256. doi:10.1016/j.tim.2015.12.011.

Conclusions

Bacteriophage therapy is an old topic that has returned to be further studied with new techniques available nowadays.

The possibilities seem endless due to the huge number of phages, and engineering techniques can overcome some of the limitations found. Some of the disadvantages are similar to those tolerated in antibiotics.

Legislation is as usual, falling behind discoveries in science and technology, and companies seek economic profit.

Bacteriophage can be an alternative or at least a help to antibiotics.

Given the current situation with resistances, more resources should be dedicated to its development.